

This led us to synthesize some new *N*-*o*-tolyl-*N'*-2-(substituted) benzothiazolyl-*N''*-alkylguanidines.

### Experimental Section

***N*-*o*-Tolyl-*N'*-2-(substituted) benzothiazolylthiocarbamides** were prepared by condensing 2-amino(substituted) benzothiazoles<sup>9,10</sup> with *o*-tolyl isothiocyanate.<sup>11</sup>

***N*-*o*-Tolyl-*N'*-2-(4-methyl)benzothiazolyl-*N''*-methylguanidine.**—*N*-*o*-Tolyl-*N'*-2-(4-methyl)benzothiazolylthiocarbamide (3.5 g), yellow PbO (4.5 g), and MeNH<sub>2</sub>-EtOH (25 ml) were heated in a

(9) A. Hegershoff, *Ber.*, **36**, 3121 (1903).

(10) P. N. Bhargava and B. T. Baliga, *J. Indian Chem. Soc.*, **35**, 807 (1958).

(11) P. N. Bhargava and P. Ram, *Indian J. Appl. Chem.*, **24**, 181 (1961).

glass autoclave on a water bath for 4 hr. After cooling, the product was boiled with EtOH (65 ml) and filtered while hot. The filtrate was concentrated and cooled when a crystalline product was obtained. It was recrystallized (EtOH) to yield white shining plates.

Similarly, other *N*-*o*-tolyl-*N'*-2-(substituted) benzothiazolyl-*N''*-alkylguanidines were prepared using MeNH<sub>2</sub>-EtOH and EtNH<sub>2</sub>-EtOH (see Table I).

**Acknowledgments.**—The authors are deeply indebted to the authorities of the Banaras Hindu University for providing the necessary facilities and also to the University Grants Commission for the award of a scholarship to one of them (H. S.).

## Book Reviews

**Steroid Hormone Analysis. Volume I.** Edited by H. CARSTENSEN. Marcel Dekker Inc., New York, N. Y. 1967. 493 pp. 22.8 × 15.0 cm.

This is the first volume of a two-volume work of ambitious proportions. It includes sections by various authors on isotopic-derivative labeling (<sup>35</sup>S), ir and nmr spectroscopy, paper chromatography of steroids, estimation of testosterone, gas chromatography, and on steroid conjugates. For the most part each section is a review of the available literature in the field with, in most cases, a natural emphasis upon the methods devised or used by the authors themselves. The authors are to be commended for the thorough job that they have done in assembling the massive literature in this field, and the book is, for the most part, a valuable compilation for experts or semiexperts who are themselves working in this area. It is hard to assess its value to the nonexpert until the second volume will have appeared.

I found the two last chapters on gas chromatography and on the analysis and identification of steroid conjugates to be the most concise and useful in this book. Thus, the former condenses a large number of references to a convenient tabular form and discusses in down-to-earth terms the major practical problems that beset investigators in this field. It can be recommended to both the expert and the nonexpert as an excellent survey complementing other reviews of the last 6 or 7 years and adding more recent experience from the author's own laboratory. The chapter on steroid conjugates was timely in that a large amount of work has been done in this field since it was last reviewed comprehensively. Both chapters refer to useful theoretical considerations underlying the techniques they review while containing a useful selection of practical points for the beginner in these fields.

While the other chapters in this book contain much more material of great interest to the expert, they leave a very patchy impression. Most of them are much too long and there are many examples of sections which read like lists of quotations from the literature of the sort seen in many *Annual Reviews* volumes. The editor rightly wished to include material from biochemistry, physiology, and chemical pathology which would give the necessary background of information on the applications of the techniques discussed by the authors. However, the balance between this type of material and accounts of analytical techniques is extremely uneven, so that some sections are devoted effectively to reviewing literature on steroid biosynthesis and metabolism. These and other sections of the book are often marred by a prolix style, serious mistakes in English, and a form of cryptic reference to the literature which is of little value to the reader. In a discussion of the secretion of androgens by the adrenal cortex, for instance, we read on p 326, "Baulieu (57) has discussed why he thinks the presence of free dehydroepiandrosterone in human adrenal vein blood may be an artifact." No further discussion of this point is made in the text, and the information content of this sentence is effectively, "Get reference 57 out of the library and see what you think of it." On p 328 we read, "Short has discussed the physiological significance of weak androgens present in adrenal vein blood (71) and we concur fully with his conclusion. With dehydroepiandrosterone matters may be different

(71)..." In the following discussion there is no further reference to Short or to his conclusion so that we are left with the impression that Short is obviously a good chap but that we had better get reference 71 out of the library if we are to find out why.

Similarly, Bojesen in the first chapter provides a number of original and stimulating discussions of the basic factors determining the precision and practicability of methods using radioactively labeled reagents. The discussion, however, is somewhat prolix and few, if any, clear guidelines emerge. It reads, in fact, rather like the unedited transcript of a first-class after-dinner dissertation which was cut short by the speaker being called to the telephone. Similarly the chapter on paper chromatography while giving a very comprehensive view of the techniques used in the author's laboratory, adds very little to the existing literature and, in fact, repeats a large amount of it at great length. While this chapter contains a number of items of interest to the expert, there is little that has not been discussed fully in the previous literature, and many of the statements and arguments are difficult to accept. Some of these can be rejected with confidence, and would be seriously misleading to newcomers to this field.

It is possible that the defects reviewed above may be remedied by the second volume when it appears, but one is left with the impression that this is not a book at all, but simply a collection of reviews. Perhaps this is a difficulty which will always be observed to some extent in books of this sort unless the editor is both fortunate in his selection of authors and extremely firm in his editing policy. The title of the book would imply that it is intended to be a text devoted to that area of analytical chemistry dealing with the measurement of steroid hormones. Such books are usually written when a field of study has been sufficiently developed to allow the authors to present reasonably concise and definite recommendations for the guidance of those who want to employ the techniques which have been developed. The present book is, in fact, a collection of reviews which might more reasonably have been called "Recent Advances in Steroid Hormone Analysis," to indicate that it is addressed more to experts interested in the development of these techniques, than to those who wish to use them. Even then, however, one is left wondering whether the material in this book should not have been published in existing journals devoted to reviews of this sort. This would have led to some very desirable pruning, and perhaps to the rejection of some of it. It remains to be noted that the printing and lay-out are excellent.

MEDICAL COLLEGE OF VIRGINIA  
RICHMOND, VIRGINIA

IAN E. BUSH

**The Structure and Function of Enzymes.** By SIDNEY A. BERNHARD. W. A. Benjamin, Inc., New York, Amsterdam. 1968. xi + 324 pp. 21 × 13.8 cm. Paperback, \$4.95. Cloth, \$10.00.

Neither the undergraduate curriculum in chemistry nor biology in American universities provides enough time or background

for students to become fully aware of the field of molecular biology which they encounter in many situations in their graduate or professional work. Chemistry students are heavily oriented toward physical chemistry without any biology, while biology majors seldom master enough organic and physical chemistry to understand the details even of the courses in oversimplified biochemistry that are offered to them in their upper-class studies. The present book has been designed to bridge this gap after a fashion, and should make for good reading for those undergraduate students whom it may "serve as a partial text for a course in biochemistry... (if they) have been exposed to introductory courses in chemical principles, organic chemistry, and cellular biology." It may just be that this book will spark an earnest effort to produce such a breed of interdisciplinary undergraduate; anyone who would try to offer lectures on enzymes at the level presented in the present book will find that he has to prepare his students at every juncture for the details of such an interdisciplinary course.

However, one has to start somewhere, and this book tries hard to lead the student from his rudimentary level to meaningful discussions which become ultimately complex and detailed enough to satisfy the expert. It begins with a survey of chemical bonds which should evoke echoes from elementary college chemistry and applies these bonds directly to protein chemistry. There follows a section on catalysis in general, which again is applied to enzyme catalysis and kinetics. This physical and analytical treatment is then expanded to more advanced topics in physical-organic chemistry pertaining to mechanistic pathways of enzyme catalysis and is ultimately capped by a long section containing many specific and up-to-date examples in which the student is introduced to details, difficulties, and apparent exceptions in this still struggling field. In between, there is a good organic chemical section on elementary protein structure, progressing from amino acid sequences to the tertiary structures of the few enzymes that have been elucidated fully. The description of the methodology used is presented particularly nicely, and the many clear and careful illustrations are a valuable feature of these chapters.

This compact and inexpensive volume should find welcome acceptance in undergraduate biochemistry courses and should be of considerable assistance to those many chemists who have never had time to immerse themselves in the area of molecular biology.

UNIVERSITY OF VIRGINIA  
CHARLOTTESVILLE, VIRGINIA

ALFRED BURGER

**The Technology of the Tetracyclines.** Edited by R. C. EVANS. Quadrangle Press, New York, N. Y. 1968. vii + 617 pp. 21 × 27 cm. \$35.00.

This book consists of a collection of excerpts from U. S. Patents which describe the commercial production of the tetracycline antibiotics along with some editorial comment. The material is divided into six chapters, one for each of the five antibiotics discussed and one devoted to cosynthesis, while each chapter is subdivided into (A) Strain Selection and Characterization, (B) Inocula Production, (C) Fermentation, (D) Recovery and Purification, (E) Assay, and (F) Physical and Chemical Properties.

The scope of the book claimed in the introduction emphasizes many of its deficiencies. Thus the statement, "This book includes all production processes for the five tetracyclines marketed in 1967," is at best a gross overstatement based on the fallacy that all production processes are described in patents. Again, the statement "as to tetracycline production technology, its history and development, the patent literature is the only source of accurate and comprehensive technical information" seems to place an inordinate amount of faith in the comprehensiveness and completeness of the patent literature. However, taken for what it is rather than what it claims to be, this compilation may provide a good starting point for the scientist or production engineer searching for a representative set of references on tetracycline production.

The book is based on 62 different patents which include the major methods of manufacture. It should not be assumed, however, that this is a complete list of patents on tetracycline technology since that list would number about 400 if one included pharmaceutical forms and mixture, chemical intermediates, and new uses.

The format makes it very difficult to differentiate between editorial comment and quotations from patents since they tend to be run together with nothing to distinguish one from the other. For example, on p 207, "It is not clear why oxytetracycline hydrochloride, when crystallized from the solvents listed above, has properties which differ appreciably from the oxytetracycline hydrochloride of commerce which is commonly crystallized from methanol." This sentence is in fact a direct quotation from U. S. Patent 2,867,661 (applied for in 1955) and not a comment by editor Evans about 1968 oxytetracycline production, although without the patent in hand it would be impossible to know this. This same sort of ambiguity is repeated continuously.

So, we repeat, in spite of the shortcomings and limitations enumerated above, a newcomer to the field of tetracycline production may find it a useful compendium.

CHEMICAL PROCESS IMPROVEMENT

T. F. SCHOLZ

ORGANIC CHEMICAL RESEARCH SECTION  
LEDERLE LABORATORIES  
PEARL RIVER, NEW YORK

J. H. BOOTHE

**Studies of a Core Curriculum.** Edited by MELVIN R. GIBSON. American Association of Colleges of Pharmacy, Silver Spring, Md. 1968. iii + 91 pp. 23 × 15.3 cm. Paperbound, \$3.50.

A committee of the American Association of Colleges of Pharmacy has defined a core content of the American pharmacy curriculum. There are five areas: pharmacognosy, pharmacology, pharmaceutical chemistry, pharmacy administration, and pharmacy. For each of these classes a detailed list of topics is given which forms the core content of recommended instruction. Although recognizing that the arrangement and intercalation of the material should be left to the individual faculty, the topics listed represent the minimum that a pharmacy student should be exposed to. For example, the topics in medicinal chemistry follow the content and arrangement in the better known modern texts on this subject.

Pharmacists who have been in the profession for more than 10 years may do well to check what minimum requirements they may not have had in their curriculum, if they decide to bring themselves up to date. Those hiring recent graduates of Colleges of Pharmacy may find that such students have covered considerable ground, more than the last generation, and that such individuals could therefore perform duties and services previously beyond the scope of pharmaceutical education.

UNIVERSITY OF VIRGINIA  
CHARLOTTESVILLE, VIRGINIA

ALFRED BURGER

**Gaddum's Pharmacology.** 6th Edition. Revised by A. S. V. BURGEN and J. F. MITCHELL. Oxford University Press, New York, N. Y. 1968. vii + 234 pp. 15.5 × 20.8 cm, including 115 illustrations. Paperbound, \$8.00.

This textbook may have been designed for medical and professional pharmacology students but it will not have much chance to take a foothold among such students in North America. The text could satisfy college students who want to explore what pharmacology may have to offer, and the semipopular style of the book, in spite of British spelling and nomenclature, could well be an incentive for this purpose. But the information needed by pharmacology students is not there; examples of such lack are too numerous to be listed. On the whole, the sections on pharmacodynamic mechanisms are more complete than those on chemotherapy which are very much deficient.

The booklet makes nice reading for the uninformed, or for those who do not have to face standard examinations in American medical schools, let alone graduate courses. Chemists totally unfamiliar with pharmacology will find it profitable as a beginner's introduction to more extensive and more competent texts.

UNIVERSITY OF VIRGINIA  
CHARLOTTESVILLE, VIRGINIA

ALFRED BURGER

**The Structural Basis of Antibody Specificity.** By DAVID PRESSMAN and ALLAN L. GROSSBERG. W. A. Benjamin, Inc., New York, N. Y. 1968. xiv + 279 pp. 23.5 × 16 cm. \$16.76.

The relation of antibody to antigen and hapten has long been recognized to parallel that of a drug to an active enzyme site or receptor, and the specificity of the antibody reaction should serve as a guide to selective drug design. The authors have summarized their long and distinguished experience in the field of immunochemical reactions in *quantitative* terms, a feature so often disregarded in molecular modification. One may regret the selection of unnatural azoproteins as the primary choice for studying structural selectivity but as a tool these azoproteins serve their purpose.

The novice is introduced to the field by a lucid and simple description of antibody-antigen and antibody-hapten combination; included are quantitative measurements of molecular areas and van der Waals radii and of the effect of hydration and other data so often ignored by those who rely essentially on vague structural analogies. The importance of the heterogeneity of antibodies is illustrated carefully, and the structure of their macromolecules is reviewed, always with the purpose of better structural design in mind. The chapter on the combining sites of antibodies should be read by all of us before we make our next speculative statement about receptor sites. A discussion of antibodies in relation to  $\gamma$ G-globulin from which they arise puts their chemical structure in the proper biological perspective. There are three appendixes summarizing the information available, and good author and subject indexes.

This book should be required reading for all medicinal chemists and for graduate students working toward a degree in this field.

UNIVERSITY OF VIRGINIA  
CHARLOTTESVILLE, VIRGINIA

ALFRED BURGER

**Medicinal Research: A Series of Monographs. Volume 3. Selected Pharmacological Testing Methods.** Edited by ALFRED BURGER. Marcel Dekker, Inc., New York, N. Y. 1968. xiv + 515 pp. 16 × 24 cm.

There will always be a need to have suitable pharmacological procedures in animals that may have relevance to therapeutic effects in humans. The third volume in this series covers twelve selected methods, some rather timely and nearly all of value. In general, the contributors have avoided the pitfalls of over-extrapolating experimental data and have collaborated to provide a useful reference text that should enjoy a fairly long shelf life.

The introductory chapter on the philosophy of pharmacological testing by Chen is followed by Dunnett's chapter on biostatistics. The latter presentation represents an attempt to condense an introductory course in biostatistics to 40 pages; I have yet to see a textbook abstracted successfully.

Four chapters are devoted to methods used for the assessment of agents acting on the central nervous system. While there are several recent reviews on the appraisal of analgetic drugs for addiction liability, Cochin's highly readable treatment conveniently includes a section on analgetic testing methods in addition. Kasé's chapter on the evaluation of antitussive agents is replete with a variety of experimental procedures and their relative merits. There is a detailed description by Tislow on the sedative hypnotic agents which correctly also includes a consideration of the anti-anxiety agents or so-called minor tranquilizers. I would have preferred a less encyclopedic and more analytical approach. Despite the wealth of information, the treatment of dependence evaluation was cursory and disappointing. In the chapter on testing of drugs for Parkinson's disease, Jenden mainly emphasizes the use of tremorine but the relationships between the tremorine method and other testing methods are briefly considered. A succinct summary of the pharmacology of tremorine and its chief metabolite, oxotremorine, is also included.

There are five chapters on evaluating drugs on certain peripheral organs and systems. Freyburger's chapter on testing for antihypertensive drugs is a relatively complete survey of the methods available. He includes a good discussion of the advantages and disadvantages of each, but more or less leaves the method of choice to the reader. Katzung's chapter on drugs affecting the contractility and electrical properties of the heart is an inclusive yet concise critique of the various methods available.

Bevan surveys briefly current methods for testing ganglionic compounds and gives an excellent detailed description of one procedure. Nechay's handling of the diuretic agents is useful for delineating gross pharmacologic properties but falls short in providing the sophisticated methodology needed to elucidate the sites of actions and the biochemic mechanisms involved. Plaa thoughtfully places liver function tests in experimental animals in proper perspective before providing numerous examples.

Study of enzyme induction by drugs has become the vogue and Mannering's account is more than a summation of the techniques that can be applied. The significance of stimulation and inhibition of drug metabolism in pharmacological testing is covered authoritatively and a comprehensive listing of agents that may influence the metabolism of other compounds is presented in tabular form. Finally, a chapter by Timiras and Vernadakis on the evaluation of drugs against radiation includes tests to protect the whole organism and specific organs and tissues.

DEPARTMENT OF PHARMACOLOGY

E. LEONG WAY

UNIVERSITY OF CALIFORNIA MEDICAL CENTER  
SAN FRANCISCO, CALIFORNIA 94122

**Pharmacological Experiments on Isolated Preparations.** By the Staff of the Department of Pharmacology, University of Edinburgh. Preface by W. L. M. Perry. E. and S. Livingstone Ltd., Edinburgh-London. 1968. ix + 131 pp. 18.8 × 24.8 cm. \$5.75 (paperback).

As interdisciplinary departments continue to multiply in colleges, universities, and in industrial laboratories, more and more chemists interested in biological happenings are learning to conduct simple biological experiments themselves. As a beginning, they try to perform tests on isolated tissues, so-called "*in vitro in vivo*" tests, since they are more easily interpreted quantitatively although their therapeutic significance may have to be viewed gingerly. The manual under review contains 30 experiments of which several are designed directly for chemistry students, and others may be used by them readily, or by medical students. No previous knowledge of pharmacological techniques is necessary, and the novice is led stepwise into experiments of increasing complexity. Among the topics covered are skeletal muscle preparations in use to measure various drug activities, various smooth muscle preparations, and nervous tissue preparations in tests for a variety of pharmacodynamic properties. Appendixes cover the practical aspects of physiological salt solutions, fiducial limits of assays, and a brief mathematical treatment of drug-receptor relationships. The booklet is illustrated richly and should be a welcome source of information as well as a "cook-book" for those medicinal chemists who want to perform some of their tests themselves, as long as they do not mind decapitating a rat and isolating the necessary tissues.

UNIVERSITY OF VIRGINIA  
CHARLOTTESVILLE, VIRGINIA

ALFRED BURGER

**The Biosynthesis of Deoxyribose.** By PETER REICHARD. John Wiley and Sons, Inc., New York, N. Y. 1968. viii + 77 pp. 13.7 × 20 cm. \$7.95.

This mini-booklet represents one of the Ciba Lectures in Biochemistry at Rutgers, The State University, and, if it had not been supported by this series, it would have appeared as a review article. It summarizes the function of the biosynthesis of deoxyribose within the biosynthesis of deoxyribonucleotides, and presents in great detail the enzymes, metabolites, and reactions involved in the formation of this important deoxypentose. A new hydrogen-transport system for the oxidoreduction of disulfide bonds, a new metabolic function of vitamin B<sub>12</sub>, and the molecular mechanism of allosteric effectors are described. This presentation may be a significant teaching tool especially for those chemists who think that the biosynthesis of an important metabolite can be disposed of by a description of the more obvious intermediates involved. It just is not so.

UNIVERSITY OF VIRGINIA  
CHARLOTTESVILLE, VIRGINIA

ALFRED BURGER

**Selective Toxicity.** Fourth Edition. By ADRIEN ALBERT. Methuen and Co., Ltd., London (distributed by Barnes and Noble, New York, N. Y.). 1968. xvii + 531 pp. 16.2 × 23.6 cm. \$14.50.

Following the third edition of this well-known text by only 3 years, the new edition can obviously not help but record so many novel events beyond those described previously. However, a comparison of the present much bulkier volume with the slender third edition of 1965 reveals that much of the "new" material should have appeared 3 years ago. Like the earlier editions, this one presents essentially principles and deductions in medicinal chemistry and does not attempt to survey drugs systematically in all the major therapeutic areas. Thus, the newer diuretics, psychopharmacologic agents, and many others that have advanced rapidly in recent years, are not even mentioned. Neither does one find one word about mathematical attempts to arrange related drugs in a meaningful way. This deletion of the application of regression analysis in its several modifications, and of bio-

statistics in drug evaluation, is the more regrettable as the book tries frankly to rationalize principles of procedure and study.

The reader will still find the many excellent generalizations of basic facts, experimental data, and ideas that have made Professor Albert's books such stimulating reading. The text is written lucidly and can be understood readily by undergraduates. The insistence on testing drugs in man at an early stage of investigation should be required reading for regulatory officials who have heaped so many roadblocks in the path of this logical step. As an inspiring teacher, the author has succeeded to single out the main guidelines of medicinal thinking. It would have been possible to include many recent applications without expanding the size of the book by deleting much ancient medicinal history which has not withstood the test of time, modern isotope and instrumental research, and the impact of those theoretical innovations which are discussed so well in other parts of these chapters.

UNIVERSITY OF VIRGINIA  
CHARLOTTESVILLE, VIRGINIA

ALFRED BURGER